AMENDMENTS TO THE DRAWINGS

Applicants request replacement of the drawings as originally filed with the the attached Replacement Drawing Sheets 1-8.

Attachment: -Replacement Drawing Sheet 1-8 (Replacing Drawing Sheets 1-9 as originally filed)

REMARKS

I. Status of the Claims

Claims 1-13 and 21-27 are pending in the application. Claims 14-20 were previously cancelled without prejudice or disclaimer. Applicants hereby amend claims 1, 2, and 4-12. Claim 13 is hereby canceled without prejudice or disclaimer. New claims 28-48 are added. Support for the above amendments can be found throughout the specification and claims of the instant application and its priority documents as originally filed. No new matter has been added.

Applicants gratefully acknowledge the Examiner's withdrawal of the previous restriction between Groups I and II on the grounds that the search for Group I provided an adequate search for the examination of Group II as well (see page 2 of Office Action).

II. Replacement Drawings

Applicants request entry of the replacement drawings submitted herewith. The replacement drawings have been submitted to improve on the clarity and legibility of the drawings as originally filed. Figure 1A has been amended to indicate the respective sequence identifiers of each depicted sequence and to highlight the position of nucleotides in each siRNA which form a mismatched base pair with the wild-type or mutant SOD1 mRNA. No new matter has been added by way of these amendments.

III. Claims Rejections -35 USC §102(e)

Claims 1-3 have been rejected under §102(e) as being anticipated by Davidson et al. (US 2005/0106731). In the opinion of the Examiner, Davidson et al. "disclose the use of siRNA to silence gene ***alleles*** involved in ALS and Huntingtons" (emphasis added).

Applicants traverse this rejection.

Applicants respectfully submit that Davidson does not teach ***allele-specific*** silencing of a target gene via RNA interference. That is, Davidson et al. does not teach one skilled in the art how to selectively silence one allele of a target gene (e.g., a mutant target allele). At best, the

disclosure of Davidson et al. is directed to ***gene-specific*** silencing using viral-based methods. For example, the Davidson et al. reference describes a "viral mediated delivery mechanism that results in *specific silencing of targeted genes*" and that "this viral mediated strategy is generally useful in *reducing expression of target genes*" (see paragraph 12, emphasis added). Davidson et al. states that this may be accomplished by designing hairpin siRNA molecules containing sequences "directed against the *gene* of interest". Nowhere does Davidson et al. provide an enabling teaching of how to conduct ***allele-specific*** silencing.

The Examiner has pointed to paragraph 100 of the Davidson reference which states: "*In some embodiments, gene silencing may be allele-specific*". Applicants submit this statement is nothing more than a mere recitation of the term "allele-specific" and does not amount to a teaching or anticipation of Applicants' claimed invention as it is totally unsupported by the remainder of the Davidson et al. reference. Davidson et al. is simply devoid of any disclosure which teaches a skilled artisan how to design an siRNA capable of allele-specific RNA interference. Indeed, Applicants note that while Davidson et al. is replete with discussion regarding viral vectors and target genes it appears to lack any teaching whatsoever regarding siRNA sequence design.

Although it is stated at paragraph 205 that "*allele-specific applications may be possible*" (emphasis added), Davidson et al. does not provide any disclosure which teaches how one skilled in the art would be able to conduct these "allele-specific applications". Moreover, this statement appears to have been made in response to the observation that an siRNA was able to discriminate between the targeted sequence of a human β-glucoronidase (βgluc) target gene and the non-target sequence of mouse β-gluc ortholog which shares 14 of 21 nucleotides or 66% sequence identity. Applicants submit that this is simply an observation of "species-specific gene silencing", a property of siRNAs that was known to those of skill in the art prior to Davidson et al. It should be noted that wild type and mutant versions of the same allele typically contain far fewer sequence differences across a 21 nucleotide portion of allelic sequence. Therefore, in contrast to gene-specific silencing, ***allele-specific*** silencing was not documented prior to Applicant's invention due to the high degree of selectivity that is required. Accordingly, Applicants invention represents an important advance in the field of RNA interference.

Moreover, Applicants note that the exemplification provided by Davidson et al. is, at best, demonstrative of only gene-specific silencing. For example, Davidson et al. exemplify ***gene-specific*** silencing of eGFP-polyglutamine fusion proteins having either a normal (eGFP-Q19) or expanded polyglutamine tract (eGFP-Q80) with viral constructs (see paragraphs 206-207). In each case, the viral constructs targeted the same eGFP portion of the fusion protein, and not the polyglutamine tract. Moreover, each fusion protein was expressed in a separate cell. As such, allele-specific silencing was clearly not demonstrated.

For at least the above reasons, Applicants submit that the disclosure of the Davidson et al. reference is clearly insufficient for a skilled artisan to conduct the claimed ***allele-specific*** methodology of the invention without undue experimentation. Accordingly, the rejection in view of Davidson et al. should be withdrawn on these grounds.

Notwithstanding the above, Applicants submit herewith a Declaration under 37 C.F.R. §1.131 (herein, "Declaration") by Drs. Zuoshang Xu and Phillip D. Zamore, co-inventors of the instant application. It is the Applicants' position that the Declaration obviates the Examiner's rejection based on Davidson et al. As described in the Declaration (filed herewith), Applicants' claimed invention was completed prior to the filing date (August 5, 2002) of Davidson et al. Applicants also note that data referenced in the Declaration is also reproduced in the working examples set forth in the specifications of the instant application and both priority documents (US Provisional Applications 60/423,507, filed November 4, 2002, and 60/488,283, filed July 18, 2003). Accordingly, for at least these additional reasons, Davidson et al. is not available for use by the Examiner as a reference, either basic or auxiliary, in the rejection of the claims of the present application under 35 U.S.C. §102(e). Therefore, it is clear that the above-quoted rejection of claims 1-3 under 35 U.S.C. §102(e) in view of Davidson et al. should be reconsidered and withdrawn.

For the avoidance of any doubt, Applicants respectfully submit that the Declaration is properly admissible to remove Davidson et al. as a prior art reference under 35 U.S.C. §102(e), since Davidson et al. ***does not currently claim the same patentable invention*** as the Applicants (see MPEP 715 (I)). Moreover, as stated in MPEP 2305 (I): "...the claims that matter for the purposes of 37 CFR 1.131 are not the published claims but the currently existing claims. For

example, if the claims that were published in a published application have been significantly modified during subsequent examination, they may no longer interfere with the rejected claims." Accordingly, since the pending claims do not conflict with the currently pending claims of Davidson et al.[1], Applicants submit that the Declaration should be entered and the reference should be removed from consideration.

IV. Claim Rejections -35 USC § 103(a)

The Examiner has rejected claims 1-13 and 21-27 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Davidson et al. [US2005/0106731], Klug et al. [European J. of Physiology, 441(6 Suppl): R205 (2001)], Brown et al. [WO 94/19493], Siddique et al. [Neurology, 47 (Suppl 2): S27-S35 (1996)], and Kunst et al. [Nature Genetics, 15: 91-94 (1996)]. Here again the Examiner relies on paragraph 100 of Davidson et al. to support the assertion that Davidson et al. have "taught that the siRNAs and shRNAs of their invention can be used to target specific alleles".

Applicants respectfully disagree with the Examiner. For at least the reasons described above, Applicants again submit that Davidson et al. does not teach one skilled in the art how to silence a specific allele of a target gene via RNA interference with any reasonable expectation of success. Moreover, Applicants submit that none of Klug et al., Brown et al., Siddique et al., or Kunst et al. provides a teaching that repairs the deficiencies of Davidson et al.

While the Examiner may be correct in stating that Davidson et al. "have taught...how to make and use siRNA and shRNAs to inhibit targeted genes in mammalian cells..." (see page 4 of Office Action, emphasis added), Applicants submit that it is incorrect to state that the same teaching applies equally to the inhibition of targeted ***alleles***. Unlike Davidson et al., the inventors of the instant application have made the surprising discovery that RNA interference can be used to specifically silence the expression of a target allele of a gene (e.g. a mutant, disease-causing allele) without substantially affecting the expression of a non-target allele of the same gene (e.g., a wild-type allele). This finding is particularly important for treating dominant

[1] See claims as filed November 20, 2006 in US App. No. 10/212,322.

gain of function disorders (e.g., ALS) where the wild-type allele plays an important biochemical function. Indeed, the inventors of the instant application discovered that RNA interference can be used to discriminate between disease and wild-type alleles which differ by as little as a single nucleotide (i.e., a point mutation). None of the cited references, either alone or in combination, teach one skilled in the art how to design siRNAs that have the selectivity required for conducting allele-specific interference.

Furthermore, as mentioned above, Applicants' Declaration establishes that Applicants' invention was completed in this country prior to the filing date of Davidson et al. (August 5, 2005). As such, Davidson et al. is not available for use by the Examiner as a reference and cannot be combined with either of Klug et al., Brown et al., Siddique et al., or Kunst et al. in the rejection of the claims of the present application. Therefore, the above-quoted rejection of claims 1-13 and 21-27 under 35 U.S.C. §103(a) in view of Davidson et al., Klug et al., Brown et al., Siddique et al., and Kunst et al. should be reconsidered and withdrawn.

CONCLUSION

In view of the above amendment and response, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

By _____

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